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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/596,196	06/17/2000	Dana A. Haley	HYS-14	1768

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EXAMINER
SCHNIZER, HOLLY G

ART UNIT	PAPER NUMBER
1653	11

DATE MAILED: 07/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No. 09/596,196	Applicant(s) HALEY ET AL.	
	Examiner Holly Schnizer	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,11,24,25,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *10,11,24,25,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

The Amendment and Response filed May 14, 2002 (Paper No. 9) has been entered and considered. Claims 19, 20, and 26 have been cancelled. Claim 31 has been added. Therefore, Claims 10, 11, 24, 25, 30, and 31 are pending and will be examined in this Office Action.

Amendment to the Specification Not Entered

In response to the objection to the recitation of amino acids in single letter code, Applicants requested that lines 24-29 of page 4 of the Specification be deleted and replaced with sequences given in three letter code. However, this amendment was not entered because the insertion would have started in the middle of a sentence. It appears that the Amendment requested was intended to replace lines 1-6 on page 5 of the Specification. Clarification of the Amendment and its placement in the Specification is requested. The objection to the Specification given in the previous Office Action is maintained.

Rejections Withdrawn

The rejection of Claims 20, 24, 25, and 30 under 35 U.S.C. 112, second paragraph as being indefinite is withdrawn in light of the amendments to the claims.

New Rejections

An updated sequence search revealed a protein with high homology and differing function to the claimed protein. Thus, upon reconsideration of the claims in light of this finding, the present claims appear to lack utility and enablement for the reasons cited below.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 10, 11, 24, 25, 30, and 31 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either an asserted utility that is specific and substantial or a well established utility.

A "substantial utility" is a utility that defines a "real world" use. Utilities that require carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. In the present case, it appears the skilled artisan would be required to carry out further research to confirm that the protein of the present invention has prothrombinase activity (thus confirming its real world context of use) for the following reasons. The asserted utilities of the claimed protein rely on the identification of the claimed protein as a prothrombinase. The identification of the protein of the present invention as a prothrombinase protein is based solely on its 37% homology to prothrombinase Fg12. However, a search of the sequence database revealed an angiopoietin protein having 99.8% homology to the protein of the present

invention (disclosed in WO 01/05825). Angiopoietins are Tie2 receptor ligands that are involved in angiogenesis (see WO 01/05825 and Jones et al. (Nature Reviews Mol. Cell. Biol. (2001) 2: 257-267). The next highest homologies are to both prothrombinase and angiopoietin proteins with similar homologies as that shown in the Specification (see sequence alignments and note that the identities appear to be lower only because they are based on the full length protein rather than only residues 98-388 as in the Specification). Thus, it appears that a sequence alignment alone does not provide a clear understanding of the function of the polypeptides of the present invention. Therefore, the asserted utilities, which rely on the prothrombinase activity of the protein, are not considered substantial since further research would be required to confirm the function and utility of the protein in light of its more significant homology to a protein of differing function.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10, 11, 24, 25, 30, and 31 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition, should Applicants establish that the asserted utilities are substantial, Applicants have not provided sufficient guidance as to how to make and use proteins that are not 100% identical to the polypeptides of SEQ ID NOs: 4 and 9. Thus, Claims 25 and 31, drawn to polypeptides with 99% homology to the claimed sequences that have prothrombinase activity, do not appear to be enabled by the Specification.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Breadth of the Claims

The claims are drawn to an isolated polypeptide having prothrombinase activity comprising an amino acid sequence 99% identical to SEQ ID NOs: 4 or 9.

Amount of direction or guidance presented

It appears that the polypeptide sequence of SEQ ID NO:4 was deduced from a polynucleotide (SEQ ID NO:3) derived from an EST sequence (see specification at pages 110-113) . All of the guidance as to the function and utility of the deduced sequence is based upon sequence homology with a prothrombinase protein (see p. 4).

The specification teaches that the polypeptide of SEQ ID NO:4 is 37% identical over 290 residues (out of 388 total amino acids) of SEQ ID NO:4 (see p. 4, lines 8-12). The specification indicates that residues 1-20 may represent a signal peptide (such that the polypeptide lacking these residues, SEQ ID NO:9, is a mature polypeptide) but state "[o]ne of skill in the art will recognize that the actual cleavage site may be different than that predicted by the computer program" (see p. 4, lines 19-21). The specification does not provide any guidance as to what amino acids may be modified that will maintain the proposed prothrombinase activity or what amino acids are essential to prothrombinase activity and cannot be modified.

Presence or Absence of working examples

There are no working examples of the polypeptides of SEQ ID NO:4 or 9 having prothrombinase activity. All information regarding the claimed polypeptides appears to be based on sequence homologies (function) and computer predictions (signal sequence). There are no working examples of a polypeptide having at least SEQ ID NO:9 or a polypeptide having 99% homology to SEQ ID NO:4 or 9 that have prothrombinase activity.

Nature of the Invention

The nature of the invention involves the unpredictable art of predicting protein function and amino acids essential to that function based solely on limited amino acid sequence alignment.

State of the Prior Art and Relative Skill of those in the art

The identification of the activity of the protein of the present invention appears to be based solely on the limited homology (37%) of the partial protein sequence (amino acids 98-388) with the Fgl2 protein shown to have prothrombinase activity (see Levy et al. U.S. Patent NO. 6,403,089, Col. 37, lines 15-67). Levy et al. indicate that the prothrombinase protein described therein is a serine protease (see Col. 4, lines 25-28) and identify serine protease sites in Fig. 5. Levy et al. do not provide any guidance regarding the location of the active site of the enzyme or even the relationship between structure (sequence) and function of the disclosed protein. And, it does not appear that the skilled artisan at the time of the invention, knew which amino acids were essential to the activity of any prothrombinase proteins. The proteins of SEQ ID NOs: 4 and 9 contain many sequence variations within the regions Levy et al. indicates as serine protease sites and do not appear to be similar in sequence to other serine proteases involved in prothrombinase activity (e.g. factor Xa). The present Specification does not provide any guidance as to the location of the active site or even the amino acids that are essential to function.

The general knowledge and level of skill in the art do not supplement the omitted description. Due to the unpredictability of predicting protein function based on amino acid sequence alone and due to the identification of an almost identical sequence as having a different function further experimentation to characterize the activity of the claimed protein is what is needed.

The prior art acknowledges that protein function predictions based solely on amino acid sequence are highly unpredictable and often wrong.

There are no art references which anticipate the claimed invention (except for sequences comprising an amino acid of SEQ ID NO:4; see below). However, the sequence database reveals a protein with an amino acid sequence that is identical to SEQ ID NO:4 except for one amino acid (see sequence alignment attached to this Office Action, Result 2 and WO 01/05825). The sequence alignment indicates that the disclosed polypeptide is angiopoietin. Angiopoietins are ligands that bind the Tie2 receptor and are involved in angiogenesis (see WO 01/05825 and Jones et al. Nature Reviews (2001) 257-267). Thus, the art teaches a polypeptide having a sequence with only one amino acid difference to that of the presently claimed SEQ ID NO:4 and a different function.

Predictability or Unpredictability of the art

The art of predicting protein function based solely on limited amino acid sequence homology is highly unpredictable as evidenced by the art. Bork et al. (Nature Genetics (1998) 18: 313-318) states "more often than not, it is clear that the cellular role of the protein in question differs from that of the detected homologue(s) and there is currently no automatic means to establish how much functional information can be legitimately transferred by analogy from the homologue to the query" (p. 315, Col. 2, last full paragraph). Smith et al. (Nature Biotechnology (1997) 15: 1222-1223) state that "[t]here are numerous cases in which proteins of very different current functions are homologous in that they evolved from a common ancestor and will match with significant sequence similarity" (p. 1222, Col. 3, second paragraph). Doerks et al. (Trends in Genetics (1998) 14(6) : 248-250) also describe the problems of assigning

function to a protein based on sequence alone and indicate that functions assigned in such a way are often erroneous.

Quantity of Experimentation Necessary

Due to the large quantity of experimentation necessary to characterize the activity of the claimed proteins (in order to verify their function and determine those amino acids involved in that function), the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention. To practice the instant invention would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues in the disclosed polypeptides that are required for the functional and structural integrity of the protein. It is this additional characterization of the protein that is required in order to obtain the functional and structural data needed to permit one to produce a protein which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation.

Conclusions

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Mon. & Thurs., 8am-5:30pm and Tues. & Wed. 9-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
July 25, 2002

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